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Electrophilic cyclization of 3-alkynyl-4-chalcogen-2-*H*-chromenes: synthesis of 3-halo-chalcogenophene[3,2-*c*]chromene derivatives

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ABSTRACT

An efficient synthesis of 3-halo-chalcogenophene[3,2-*c*]chromene has been accomplished via electrophilic cyclization reaction of 3-alkynyl-4-chalcogen-2*H*-chromene using I_2, PhSeBr, and $BuTeBr_3$ as electrophilic sources. The cyclization reaction proceeded cleanly under mild reaction conditions, and 3-halochalcogen-chromenes were formed in good yields. In addition, the obtained 3-iodo-chalcogenophene-chromenes were readily transformed to more complex products using a metal–halogen exchange reaction with *n*-BuLi and trapping the lithium-intermediate formed with aldehyde, furnishing the desired secondary alcohol in good yield. Conversely, using the palladium catalyzed cross-coupling reactions with terminal alkynes and boronic acid, we were able to obtain the Sonogashira and Suzuki type products in good yields.

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Chalcogenides are widely studied agents with a diverse array of biological effects.[1] These include potent antitumor and antiviral activities as well as efficacy as a maturation inducing agent.[2] Among chalcogenides, the fused chalcogenophene derivatives play an important role in organic synthesis because of their excellent electrical properties and environmental stability. Chalcogenophene oligomers are compounds of current interest because many of them show photoenhanced biological activities[3] and crystalline polymerizations.[4] Thus, a wide variety of oligomers and related chalcogen compounds including mixed thiophene-pyrrole oligomers have been synthesized mainly with the expectation of obtaining excellent precursor compounds for molecular devices and electroconductive polymers.[5]

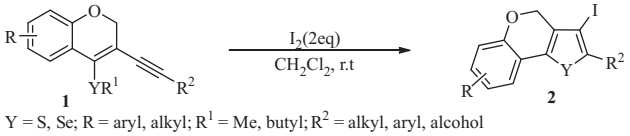
The derivatives of multiple heterocycles are valued not only for their rich and varied chemistry, but also for many important biological properties.[5] The synthesis of multiple heterocycles has also attracted considerable attention because of their use for the synthesis of a variety of functional materials for electronic devices.[6,7] However, little is known about the multiple Se-(*S*)-chromene nucleus with different features and applications in the literature, and there are only a few reports of a generally useful synthesis of multiple seleno-thiophenes.[8]

In the context of heterocycles, electrophilic cyclization of unsaturated compounds has proved to be an efficient method for one-step construction of a substituted heterocyclic unit.[5] Important heterocycles, such as indoles,[9a,b] benzo[*b*]furans,[9c,d] benzo[*b*]thiophenes,[9e,f] benzo[*b*]selenophenes,[9g] thiophenes,[9h] furans,[9i] and pyrroles[9j] among others[9k–v] have been accessed using this protocol.[9]

These and especially the knowledge that multiple Se-(*S*)-chromene nuclei are promising candidates for biological active compounds or pharmaceuticals prompted us to develop a complete investigation on the electrophilic cyclization of 3-alkynyl-4-chalcogen-2*H*-chromenes **1** to obtain the 3-halo-chalcogenophene-chromenes **2** as the sequence showed in Scheme 1.

The starting 3-alkynyl-4-chalcogen-2*H*-chromene **1** was readily available by Sonogashira cross-coupling reactions of 3-iodo-4-chalcogen-2*H*-chromene derivatives with different terminal alkynes.[10]

As preliminary studies, we examined the feasibility of the electrophilic cyclization reaction with I_2 and ICl, as electrophilic sources, by using 3-phenylethynyl-6-methyl-4-butylselenyl-2*H*-chromene **1a** as substrate, in order to determine the optimum reaction conditions (Table 1). Treatment of **1a** with I_2 (2 equiv), using THF as solvent at room temperature furnished the cyclized product **2a** in 70% yield (Table 1, entry 1). Encouraged by this result, we further investigated the reaction behavior with other solvents and electrophilic sources with the aim to improve the protocol. To identify the solvent potentially suitable for the cycliza-



Y = S, Se; R = aryl, alkyl; R^1 = Me, butyl; R^2 = alkyl, aryl, alcohol

Scheme 1. General scheme.

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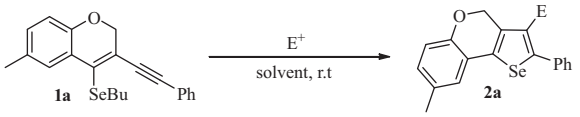
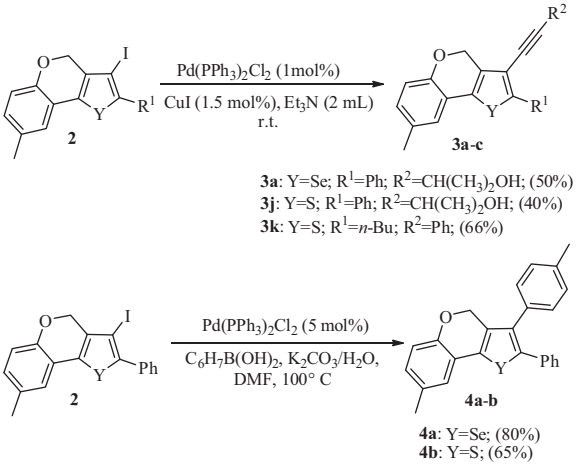
Table 1
Effect of reaction conditions for the cyclization reaction



Entry	E^+	E^+ (equiv)	Solvent	Yield[a] (%)
1	I_2	2.0	THF	70
2	I_2	2.0	CH_3CN	73
3	I_2	1.1	CH_2Cl_2	94
4	I_2	3.0	CH_2Cl_2	97
5	I_2	2.0	CH_2Cl_2	99
6	I_2	2.0	Hexane	nr
7	ICl	1.1	CH_2Cl_2	86
8	ICl	1.5	CH_2Cl_2	63
9	ICl	2.0	CH_2Cl_2	49

[a] Yields were determined by GC analysis.



Scheme 2. Reactivity of **2** toward Sonogashira and Suzuki cross-coupling.

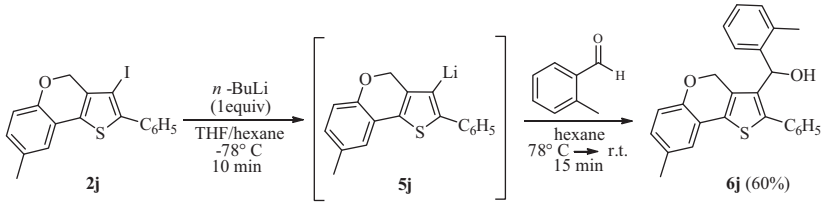
tion, we chose CH_2Cl_2, MeCN, and hexane. For this process, CH_2Cl_2 was the most effective solvent giving the cyclized product in 99% yield (Table 1, entry 5). The study to screen the electrophile source showed that ICl gave the target products in lower yields than I_2 (Table 1, entries 7–9). It is important to note that when the amount of I_2 was increased from 1.0 to 3.0 equiv the desired product was obtained in similar yields (Table 1, entry 4). The analysis of the optimized reactions revealed that the optimum conditions for this electrophilic cyclization were the use of 4-butylselenyl-2*H*-chromene **1a** (0.25 mmol), I_2 (2.0 equiv) in CH_2Cl_2 (5 ml) at room temperature. Using this methodology we were able to prepare 3-iodoselenopheno[3,2-*c*]chromene **2a** in almost quantitative yield.

After optimizing the reaction parameters, the functional group tolerance was explored. The results are presented in Table 2. Many functional groups were compatible with the reaction conditions. In general, all the reactions proceeded smoothly with good results. Most importantly, the cyclization turned out to be general with respect to a diverse array of functionalities. The experiments showed that the electrophilic cyclization of substrates having aryl or alkyl group bonded to alkyne formed the desired products in similar yields (Table 2, entries 1 and 2). In addition, the reaction with bulky alkyl substituents also led to the formation of the desired product, however, a decrease in the yield was observed (Table 2, entry 3). A significant decrease in yield of 3-halo-chalcogenophene chromene was also observed when the reaction was performed with a bulky propargyl alcohol derivative (Table 2, entry 4). In the case of substrates with different substituents in the chromene ring, our reaction system was also suitable for the cyclization of both naphtho and aryl substituents giving the desired cyclized products in good yields (Table 2, entries 8 and 9). In addition to the use of I_2 as electrophile source, the reaction with $BuTeBr_3$ and PhSeBr also led to the formation of the desired products in 58% and 60% yield, respectively (Table 2, entries 14 and 15). This result is significant particularly when one considers that there are many ways to transform the resulting tellurium and selenium functionalities into other substituents. It is also worth noting that this reaction can be performed using not only selenium as the nucleophile but also sulfur groups (Table 2, entries 10–13).

This approach to 3-halo-chalcogenophene-chromenes **2** provides a very useful synthesis of various substituted 3-chromenes via elaboration of the resulting iodide functionality into other substituents. For instance, the resulting 3-iodo-chalcogenophene-chromenes **2** are particularly useful intermediates in many palladium-catalyzed processes, such as Sonogashira, Suzuki, and Heck cross couplings. In view of this, compound **2** was treated under standard Sonogashira,[11] Suzuki[12] conditions, providing the corresponding coupling products **3** and **4**, respectively, in moderate to good yields (Scheme 2).

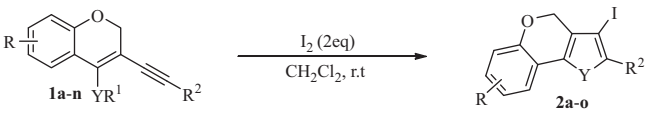
In addition to the palladium catalyzed cross coupling reactions, we have carried out the halogen-lithium exchange reaction of product **2j** with *n*-butyllithium. Metal–halogen exchange reactions have great importance in synthetic organic chemistry, particularly with respect to the formation of new C–C bonds.[13] Analogous to the well-known metal-halogen exchange reactions, which lead to a lithium intermediate, we extended this finding to obtain an intermediate 3-lithio-chalcogenophene-chromene **5j**. In this way, performing the reaction of **2j** with *n*-BuLi (1 equiv) in a mixture of hexane (2 mL) and THF (2 mL) at −78 °C followed by the addition of aldehyde (1 equiv), the secondary alcohol **6j** was obtained in 60% yield (Scheme 3).

In summary, we have demonstrated the electrophilic cyclization reaction of 3-alkynyl-4-chalcogen-2*H*-chromenes with different electrophilic sources under exceptionally mild conditions and established a route to obtain 3-halo-chalcogenophene-chromenes **2** in good yields. The 3-iodo-4-chalcogenophene-chromenes obtained by electrophilic cyclization appear highly promising as intermediates for the preparation of more highly substituted structures. In fact, using the palladium catalyzed cross-coupling reactions with terminal alkynes and boronic acids we were able to convert the 3-iodo-4-chalcogenophene-chromene in highly



Scheme 3. Reactivity of **2j** toward *n*-BuLi followed by aldehyde.

Table 2
Scope and generality of the electrophilic cyclization of 3-halo-chalcogenophene[3,2-*c*]chromene



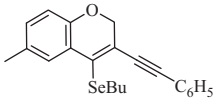
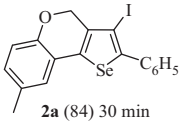
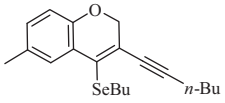
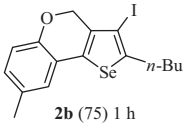
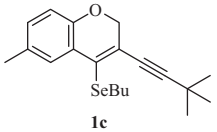
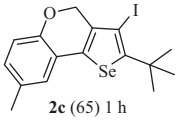
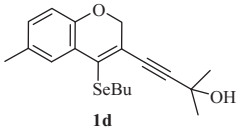
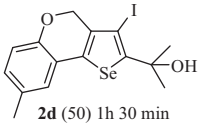
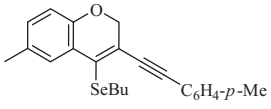
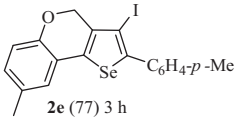
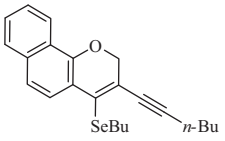
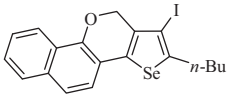
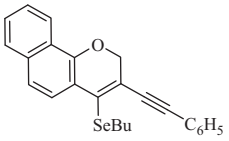
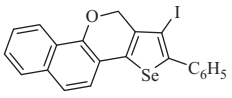
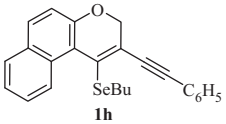
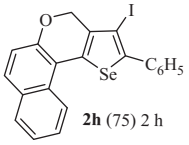
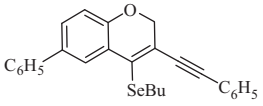
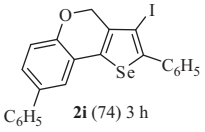
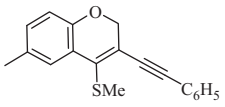
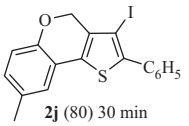
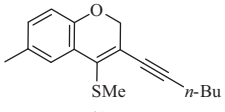
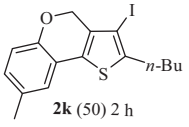
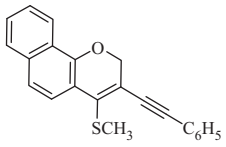
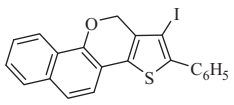
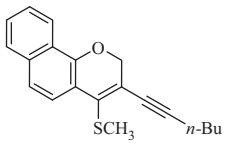
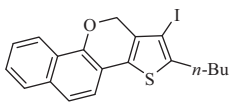
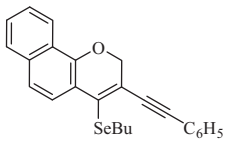
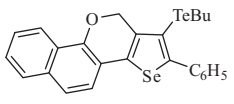
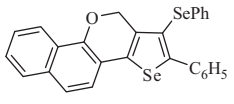
Entry	Substrate	Product yields[a] (%)/time
1	 **1a**	 **2a** (84) 30 min
2	 **1b**	 **2b** (75) 1 h
3	 **1c**	 **2c** (65) 1 h
4	 **1d**	 **2d** (50) 1h 30 min
5	 **1e**	 **2e** (77) 3 h
6	 **1f**	 **2f** (86) 15 min
7	 **1g**	 **2g** (84) 30 min
8	 **1h**	 **2h** (75) 2 h
9	 **1i**	 **2i** (74) 3 h
10	 **1j**	 **2j** (80) 30 min
11	 **1k**	 **2k** (50) 2 h

Table 2 (*continued*)

Entry	Substrate	Product yields[a] (%)/time
12	 **1l**	 **2l** (55) 15 min
13	 **1m**	 **2m** (65) 2 h
14	 **1n**	 **2n** (58) 2 h
15	1n	 **2o** (60) 15 min

[a] Yields are given for isolated products.

substituted multiple chalcogenophenes in good yields. Conversely, 3-iodo-4-chalcogenophene-chromene was treated under metal–halogen exchange conditions with *n*-BuLi, and trapping the intermediates with aldehydes provided the corresponding secondary alcohol in good yields. We believe that this approach to 3-iodo-4-chalcogenophene-chromenes should prove quite useful in synthesis, particularly when one considers that there are many ways to transform the resulting halogen, tellurium, and selenium functionalities into other substituents.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.049.

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